

Preclinical development of a pan Bcl2 inhibitor for cancer stem cell directed therapy

Grant Award Details

Preclinical development of a pan Bcl2 inhibitor for cancer stem cell directed therapy

Grant Type: Early Translational II

Grant Number: TR2-01789

Project Objective: To achieve a development candidate for treatment of leukemias using a targeted therapy that inhibits BCL2 gene family which plays a critical role in cancer stem cell survival

Investigator:

Name:	Catriona Jamieson
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Blood Cancer, Cancer

Human Stem Cell Use: Cancer Stem Cell

Cell Line Generation: Cancer Stem Cell

Award Value: \$3,103,041

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Grant Application Details

Application Title: Preclinical development of a pan Bcl2 inhibitor for cancer stem cell directed therapy

Public Abstract: Cancer is the leading cause of death for individuals under 85. Relapse and metastatic disease are the leading causes of cancer related mortality. Anti-apoptotic BCL2 family member overexpression has been shown to promote disease progression in both chronic myeloid leukemia (CML) and prostate cancer. And, the emergence of cancer stem cells (CSC) promotes apoptosis resistance in the bone marrow metastatic microenvironment. While targeted therapy with BCR-ABL inhibitors has improved survival of patients with chronic phase CML, the prevalence has doubled since 2001 with over 22,000 people living with CML in the US in 2009. Unfortunately, a growing proportion of patients become intolerant or simply cannot afford full dose BCR-ABL inhibitor therapy and thus, progress to advanced phase disease with a 5 year survival rate of less than 30%. Although prostate cancer prevalence was high at 2.26 million in 2007, distant disease was relatively rare at 5%. However, like blast crisis CML, metastatic prostate cancer survival was only 30% over 5 years.

Overexpression of B-cell lymphoma/leukemia-2 (BCL2) family genes has been observed in human blast crisis CML and advanced prostate cancer and may fuel CSC survival. Recent RNA sequencing data demonstrate that human CSC express a panoply of anti-apoptotic Bcl-2 isoforms in response to extrinsic signals in vivo, indicating that a pan BCL2 inhibitor will be required to abrogate CSC survival. Through binding and anti-tumor studies, a potent inhibitor of BCL2 pro-survival family proteins, BI-97C1, has been identified which inhibits the binding of BH3 peptides to Bcl-XL, Bcl-2, Mcl-1 and Bfl-1 with nanomolar IC₅₀ values. Notably, BI-97C1 potently inhibits growth of human prostate cancer in a xenograft model as well as blast crisis CML CSC engrafted in RAG2-/- μ C-/- mice while exerting minimal cytotoxicity toward bax-/-bak-/- cells. Because BI-97C1 inhibits all six anti-apoptotic Bcl-2 family members including Bcl-2, Mcl-1 (myeloid cell leukemia 1), Bcl-XL (BCL2L1), Bfl-1 (BCL-2A1), Bcl-W (BCL2L2) and Bcl-B (BCL2L10) proteins, with improved chemical, plasma and microsomal stability relative to apogossypol, we anticipate that it will have clinical utility for targeting apoptosis resistant human CSC in two malignancies with proven reliance on BCL2 signaling – blast crisis CML and advanced prostate cancer.

Thus, anti-apoptotic BCL2 family member inhibition with BI-97C1 could represent a vital component of a potentially curative strategy for advanced malignancies that may obviate the need for costly continuous tyrosine kinase inhibitor therapy by increasing sensitivity to therapy. Elimination of CSC contributing to therapeutic resistance, the primary cause of cancer death, is of high clinical importance and thus, development of a small molecule pan-BCL2 inhibitor would fulfill a vital unmet medical need, fuel California biotechnology stem cell R&D efforts and decrease health care costs for patients with cancer.

**Statement of Benefit to
California:**

Cancer is the leading cause of death for individuals under 85 and usually results from metastatic disease in the setting of therapeutic recalcitrance. Anti-apoptotic BCL2 family member overexpression has been shown to promote disease progression in both chronic myeloid leukemia and prostate cancer. Moreover, the emergence of quiescent cancer stem cells promotes apoptosis resistance in the bone marrow niche for. While targeted BCR-ABL inhibition has resulted in improved survival of patients with chronic phase CML, the prevalence has doubled since 2001 with over 22,000 people living with CML in the US in 2009 (<http://www.leukemia-lymphoma.org>). Unfortunately, a growing proportion of patients become intolerant or simply cannot afford full dose BCR-ABL inhibitor therapy as a result of spiraling annual costs and thus, progress to advanced phase disease with a 5 year survival rate of less than 30%. Although prostate cancer prevalence was high at 2.26 million in 2007, distant disease was relatively rare at 5%. Like CML, metastatic prostate cancer survival was only 30% over 5 years (<http://seer.cancer.gov/statfacts/html/prost.html#prevalence> <<http://seer.cancer.gov/statfacts/html/prost.html#prevalence>>). Like blast crisis CML, prostate cancer progression and metastasis is associated with BCL2 overexpression. Thus, anti-apoptotic BCL2 family member inhibition with BI-97C1 could represent a vital component of a potentially curative strategy for advanced malignancies that may obviate the need for costly continuous tyrosine kinase inhibitor therapy by increasing sensitivity to therapy. Elimination of CSC contributing to therapeutic resistance, the primary cause of cancer death, is of high clinical importance and thus, development of a small molecule pan-BCL2 inhibitor would fulfill a vital unmet medical need, fuel California biotechnology stem cell R&D efforts and decrease health care costs for patients with cancer.

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